(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 November 2004 (11.11.2004)

PCT

(10) International Publication Number
WO 2004/096799 A1

(51) International Patent Classification[7]: C07D 451/02, A61K 31/46

(21) International Application Number: PCT/EP2004/004375

(22) International Filing Date: 26 April 2004 (26.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/EP03/04490 30 April 2003 (30.04.2003) EP

(71) Applicant *(for all designated States except US)*: **ACTELION PHARMACEUTICALS LTD** [CH/CH]; Gewerbestrasse 16, CH-4123 Allschwil (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BEZENCON, Olivier** [CH/CH]; Dürrenmattweg 53, CH-4123 Allschwil (CH). **BUR, Daniel** [CH/CH]; Im Rosengarten 24, CH-4106 Therwil (CH). **FISCHLI, Walter** [CH/CH]; Obertorweg 64, CH-4123 Allschwil (CH). **REMEN, Lubos** [SK/CH]; Kurzelängeweg 28, CH-4123 Allschwil (CH). **RICHARD-BILDSTEIN, Sylvia** [FR/FR]; 12, rue des Beaux Prés, F-68440 Dietwiller (FR). **WELLER, Thomas** [CH/CH]; Hoczlistrasse 58, CH-4102 Binningen (CH). **SIFFERLEN, Thierry** [FR/FR]; 6, rue de Thann, F-68116 Guewenheim (FR).

(74) Agent: **HOFMANN, Dieter**; Therwilerstrasse 87, CH-4153 Reinach (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TROPANE DERIVATIVES AND THEIR USE AS ACE INHIBITORS

(57) Abstract: The invention relates to novel tropane derivatives and related compounds and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as inhibitors of renin.

WO 2004/096799 A1

TROPANE DERIVATIVES AND THEIR USE AS ACE INHIBITORS

The invention relates to novel compounds of the general formula I. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula I and especially their use as renin inhibitors in cardiovascular events and renal insufficiency. Furthermore, these compounds can be regarded as inhibitors of other aspartyl proteases and might therefore be useful as inhibitors of plasmepsins to treat malaria and as inhibitors of *Candida albicans* secreted aspartyl proteases to treat fungal infections.

In the renin-angiotensin system (RAS) the biologically active angiotensin II (Ang II) is generated by a two-step mechanism. The highly specific enzyme renin cleaves angiotensinogen to angiotensin I (Ang I), which is then further processed to Ang II by the less specific angiotensin-converting enzyme (ACE). Ang II is known to work on at least two receptor subtypes called AT_1 and AT_2. Whereas AT_1 seems to transmit most of the known functions of Ang II, the role of AT_2 is still unknown.

Modulation of the RAS represents a major advance in the treatment of cardiovascular diseases. ACE inhibitors and AT_1 blockers have been accepted to treat hypertension (Waeber B. *et al.*, "The renin-angiotensin system: role in experimental and human hypertension", in Berkenhager W. H., Reid J. L. (eds): *Hypertension*, Amsterdam, Elsevier Science Publishing Co, **1996**, 489-519; Weber M. A., *Am. J. Hypertens.*, **1992**, *5*, 247S). In addition, ACE inhibitors are used for renal protection (Rosenberg M. E. *et al.*, *Kidney International*, **1994**, *45*, 403; Breyer J. A. *et al.*, *Kidney International*, **1994**, *45*, S156), in the prevention of congestive heart failure (Vaughan D. E. *et al.*, *Cardiovasc. Res.*, **1994**, *28*, 159;

Fouad-Tarazi F. *et al.*, *Am. J. Med.*, **1988**, *84 (Suppl. 3A)*, 83) and myocardial infarction (Pfeffer M. A. *et al.*, *N. Engl. J. Med.*, **1992**, *327*, 669).

The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, *9*, 645). The only substrate known for renin is angiotensinogen, which can only be processed (under physiological conditions) by renin. In contrast, ACE can also cleave bradykinin besides Ang I and can be by-passed by chymase, a serine protease (Husain A., *J. Hypertens.*, **1993**, *11*, 1155). In patients inhibition of ACE thus leads to bradykinin accumulation causing cough (5-20%) and potentially life-threatening angioneurotic edema (0.1-0.2%) (Israili Z. H. *et al.*, *Annals of Internal Medicine*, **1992**, *117*, 234). Chymase is not inhibited by ACE inhibitors. Therefore, the formation of Ang II is still possible in patients treated with ACE inhibitors. Blockade of the AT_1 receptor (e.g. by losartan) on the other hand overexposes other AT-receptor subtypes to Ang II, whose concentration is dramatically increased by the blockade of AT_1 receptors. This may raise serious questions regarding the safety and efficacy profile of AT_1 receptor antagonists. In summary, renin inhibitors are not only expected to be different from ACE inhibitors and AT_1 blockers with regard to safety, but more importantly also with regard to their efficacy to block the RAS.

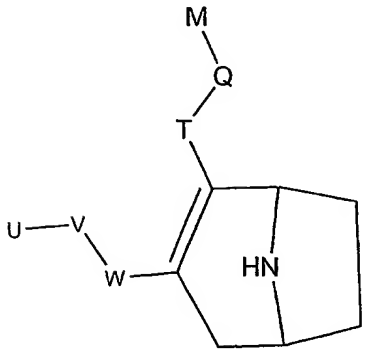
Only limited clinical experience (Azizi M. *et al.*, *J. Hypertens.*, **1994**, *12*, 419; Neutel J. M. *et al.*, *Am. Heart*, **1991**, *122*, 1094) has been created with renin inhibitors because of their insufficient oral activity due to their peptidomimetic character (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, *9*, 645). The clinical development of several compounds has been stopped because of this problem together with the high cost of goods. Only one compound containing four chiral centers has entered clinical trials (Rahuel J. *et al.*, *Chem. Biol.*, **2000**, *7*, 493; Mealy N. E., *Drugs of the Future*, **2001**, *26*, 1139). Thus, metabolically stable, orally bioavailable and sufficiently soluble renin inhibitors that can be prepared on a large scale are missing and sought. Recently, the first non-peptide renin inhibitors were described which show high *in vitro* activity (Oefner C. *et al.*, *Chem. Biol.*, **1999**, *6*, 127; Patent Application WO97/09311; Märki H. P. *et al.*, *Il*

Farmaco, **2001**, *56*, 21). However, the development status of these compounds is not known.

The present invention relates to the identification of renin inhibitors of a non-peptidic nature and of low molecular weight. Orally active renin inhibitors of long duration of action which are active in indications beyond blood pressure regulation where the tissular renin-chymase system may be activated leading to pathophysiologically altered local functions such as renal, cardiac and vascular remodeling, atherosclerosis, and possibly restenosis are described.

The present invention describes non-peptidic renin inhibitors.

In particular, the present invention relates to novel compounds of the general formula **I**,



Formula **I**

wherein

W is a six-membered, non benzofused, phenyl or heteroaryl ring, substituted by V in *meta* or *para* position;

V represents a bond; $-(CH_2)_r-$; $-A-(CH_2)_s-$; $-CH_2-A-(CH_2)_t-$; $-(CH_2)_s-A-$; $-(CH_2)_2-A-(CH_2)_u-$; $-A-(CH_2)_v-B-$; $-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-B-$; $-CH_2-CH_2-CH_2-A-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-CH_2-$; $-CH_2-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-CH_2-B-$; -

CH_2-CH_2-A-CH_2-CH_2-B-; -O-CH_2-CH(OCH_3)-CH_2-O-; -O-CH_2-CH(CH_3)-CH_2-O-; -O-CH_2-CH(CF_3)-CH_2-O-; -O-CH_2-C(CH_3)$_2$-CH_2-O-; -O-CH_2-C(CH_3)$_2$-O-; -O-C(CH_3)$_2$-CH_2-O-; -O-CH_2-CH(CH_3)-O-; -O-CH(CH_3)-CH_2-O-; -O-CH_2-C(CH_2CH_2)-O-; or -O-C(CH_2CH_2)-CH_2-O-;

A and B independently represent -O-; -S-; -SO-; -SO_2-;

U represents aryl; heteroaryl;

T represents -$CONR^1$-; -$(CH_2)_pOCO$-; -$(CH_2)_pN(R^1)CO$-; -$(CH_2)_pN(R^1)SO_2$-; or -COO-;

Q represents lower alkylene; lower alkenylene;

M represents hydrogen; cycloalkyl; aryl; heterocyclyl; heteroaryl;

R^1 represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

p is the integer 1, 2, 3 or 4;
r is the integer 3, 4, 5, or 6;
s is the integer 2, 3, 4, or 5;
t is the integer 1, 2, 3, or 4;
u is the integer 1, 2, or 3;
v is the integer 2, 3, or 4;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

In the definitions of general formula I – if not otherwise stated – the term **lower alkyl**, alone or in combination with other groups, means saturated, straight and branched chain groups with one to seven carbon atoms, preferably one to four carbon atoms that can be optionally substituted by halogens. Examples of lower alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and heptyl. The methyl, ethyl nad isopropyl groups are preferred.

The term **lower alkoxy** refers to a R-O group, wherein R is a lower alkyl. Examples of lower alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy, iso-butoxy, sec-butoxy and tert-butoxy.

The term **lower alkenyl**, alone or in combination with other groups, means straight and branched chain groups comprising an olefinic bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkenyl are vinyl, propenyl or butenyl.

The term **lower alkinyl**, alone or in combination with other groups, means straight and branched chain groups comprising a triple bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkinyl are ethinyl, propinyl or butinyl.

The term **lower alkylene**, alone or in combination with other groups, means straight and branched divalent chain groups with one to seven carbon atoms, preferably one to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkylene are ethylene, propylene or butylene.

The term **lower alkenylene**, alone or in combination with other groups, means straight and branched divalent chain groups comprising an olefinic bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms, that

can be optionally substituted by halogens. Examples of lower alkenylene are vinylene, propenylene and butenylene.

The term **lower alkylenedioxy**, refers to a lower alkylene substituted at each end by an oxygen atom. Examples of lower alkylenedioxy groups are preferably methylenedioxy and ethylenedioxy.

The term **lower alkylenoxy** refers to a lower alkylene substituted at one end by an oxygen atom. Examples of lower alkylenoxy groups are preferably methylenoxy, ethylenoxy and propylenoxy.

The term **halogen** means fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine and bromine.

The term **cycloalkyl** alone or in combination, means a saturated cyclic hydrocarbon ring system with 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, which can be optionally mono- or multisubstituted by lower alkyl, lower alkenyl, lower alkenylene, lower alkoxy, lower alkylenoxy, lower alkylenedioxy, hydroxy, halogen, $-CF_3$, $-NR^1R^{1'}$, $-NR^1C(O)R^{1'}$, $-NR^1S(O_2)R1'$, $-C(O)NR^1R^{1'}$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^{1'}$ whereby $R^{1'}$ represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl. The cyclopropyl group is a preferred group.

The term **aryl**, alone or in combination, relates to the phenyl, the naphthyl or the indanyl group, preferably the phenyl group, which can be optionally mono- or multisubstituted by lower alkyl, lower alkenyl, lower alkinyl, lower alkenylene or lower alkylene forming with the aryl ring a five- or six-membered ring, lower alkoxy, lower alkylenedioxy, lower alkylenoxy, hydroxy, hydroxy-lower alkyl, halogen, cyano, $-CF_3$, $-OCF_3$, $-NR^1R^{1'}$, $-NR^1R^{1'}$ - lower alkyl, $-NR^1C(O)R^{1'}$, $-NR_1S(O_2)R^1$, $-C(O)NR^1R^{1'}$, $-NO_2$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$,

$-SO_2R^1$, $-SO_2NR^1R^{1'}$, benzyloxy, whereby $R^{1'}$ has the meaning given above. Preferred substituents are halogen, lower alkoxy, lower alkyl, CF_3, OCF_3.

The term **aryloxy** refers to an Ar-O group, wherein Ar is an aryl. An example of a lower aryloxy group is phenoxy.

The term **heterocyclyl**, alone or in combination, means saturated or unsaturated (but not aromatic) five-, six- or seven-membered rings containing one or two nitrogen, oxygen or sulfur atoms which may be the same or different and which rings can be optionally substituted with lower alkyl, hydroxy, lower alkoxy and halogen. The nitrogen atoms, if present, can be substituted by a $-COOR^2$ group. Examples of such rings are piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, 1,4-dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dihydropyrrolyl, imidazolidinyl, dihydropyrazolyl, pyrazolidinyl, dihydroquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl.

The term **heteroaryl**, alone or in combination, means six-membered aromatic rings containing one to four nitrogen atoms; benzofused six-membered aromatic rings containing one to three nitrogen atoms; five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; benzofused five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; five-membered aromatic rings containing one oxygen and one nitrogen atom and benzofused derivatives thereof; five-membered aromatic rings containing a sulfur and a nitrogen or an oxygen atom and benzofused derivatives thereof; five-membered aromatic rings containing two nitrogen atoms and benzofused derivatives thereof; five-membered aromatic rings containing three nitrogen atoms and benzofused derivatives thereof, or a tetrazolyl ring. Examples of such ring systems are furanyl, thiophenyl, pyrrolyl, pyridinyl, pyrimidinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazinyl, thiazolyl, isothiazolyl, pyridazinyl, pyrazolyl, oxazolyl, isoxazolyl, coumarinyl, benzothiophenyl, quinazolinyl, quinoxalinyl. Such rings may be adequatly substituted with lower alkyl, lower alkenyl, lower alkinyl, lower alkylene, lower alkenylene, lower

alkylenedioxy, lower alkyleneoxy, hydroxy-lower alkyl, lower alkoxy, hydroxy, halogen, cyano, $-CF_3$, $-OCF_3$, $-NR^1R^{1'}$, $-NR^1R^{1'}$ - lower alkyl, $-N(R^1)COR^1$, $-N(R^1)SO_2R^1$, $-CONR^1R^{1'}$, $-NO_2$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^{1'}$, another aryl, another heteroaryl or another heterocyclyl and the like, whereby $R^{1'}$ has the meaning given above. Preferred heteroaryl are pyridinyl, pirimidinyl, pirazinyl.

The term **heteroaryloxy** refers to a Het-O group, wherein Het is a heteroaryl.

The expression **pharmaceutically acceptable** salts encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, and the like that are non toxic to living organisms or in case the compound of formula **I** is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like.

Compounds of the invention also include nitrosated compounds of the general formula **I** that have been nitrosated through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulffiydryl condensation) and/or nitrogen. The nitrosated compounds of the present invention can be prepared using conventional methods known to one skilled in the art. For example, known methods for nitrosating compounds are described in U.S. Pat. Nos. 5,380,758 and 5,703,073; WO 97/27749; WO 98/19672; WO 98/21193; WO 99/00361 and Oae et al, Org. Prep. Proc. Int., 15(3): 165-198 (1983), the disclosures of each of which are incorporated by reference herein in their entirety.

The compounds of the general formula **I** can contain two or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form and pharmaceutically acceptable salts thereof.

The present invention encompasses all these forms. Mixtures may be separated in a manner known *per se*, i.e. by column chromatography, thin layer chromatography, HPLC or crystallization.

A group of preferred compounds of general formula **I** above are those wherein W, V, and U are as defined in general formula **I** and

T is $-CONR^1-$;
Q is methylene;
M is aryl; heteroaryl.
Another group of even more preferred compounds of general formula **I** are those wherein W, U, T, Q, and M are as defined in general formula **I** above and

V is $-CH_2CH_2O-$; $-CH_2CH_2CH_2O-$; $-OCH_2CH_2O-$.

Another group of also more preferred compounds of general formula I are those wherein V, U, T, Q, and M are as defined in general formula **I** above and

W represents a 1,4-disubstituted phenyl group.

Another group of also more preferred compounds of general formula **I** are those wherein W, V, U, T, Q, and M are as defined in general formula **I** above and

U is a mono-, di-, or trisubstituted phenyl or heteroaryl, wherein the substituents are halogen, lower alkyl, lower alkoxy, CF_3.

Especially preferred compounds of general formula **I** are those selected from the group consisting of:

(*rac.*)-(*1R**, *5S**)-3-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-8-azabicyclo-[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*rac.*)-(*1R**, *5S**)-3-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*rac.*)-(*1R**, *5S**)-3-{4-[3-(4-fluoro-5-methylisoxazol-3-yloxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(3-methoxy-2-methyl-benzyl)amide.

The compounds of general formula **I** and their pharmaceutically acceptable salts may be used as therapeutics e.g. in form of pharmaceutical compositions. These pharmaceutical compositions containing at least one compound of general formula **I** and usual carrier materials and adjuvants may especially be used for the treatment or prophylaxis of disorders which are associated with a dysregulation of the renin angiotensin system (RAS), comprising cardiovascular and renal diseases. Examples of such diseases are hypertension, congestive heart failure, pulmonary heart failure, coronary diseases, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, and renal failure. They can also be used to prevent restenosis after balloon or stent angioplasty, to treat erectile dysfunction, glomerulonephritis, renal colic, and glaucoma. Furthermore, they can be used in the therapy and the prophylaxis of diabetic complications, complications after vascular or cardiac surgery, complications of treatment with immunosuppresive agents after organ transplantation, complications of cyclosporin treatment, as well as other diseases presently known to be related to the RAS.

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are related to the RAS such as hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppresive agents after organ transplantation, and other diseases which are related to the RAS, which method comprises administering a compound according of formula I to a human being or animal.

The invention further relates to the use of compounds of general formula **I** as defined above for the treatment and/or prophylaxis of diseases which are associated with the RAS such as hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppresive agents after organ transplantation, and other diseases presently known to be related to the RAS.

In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with the RAS such as hypertension, coronary diseases, cardiac insufficiency, renal insufficiency, renal and myocardial ischemia, and renal failure. These medicaments may be prepared in a manner known per se.

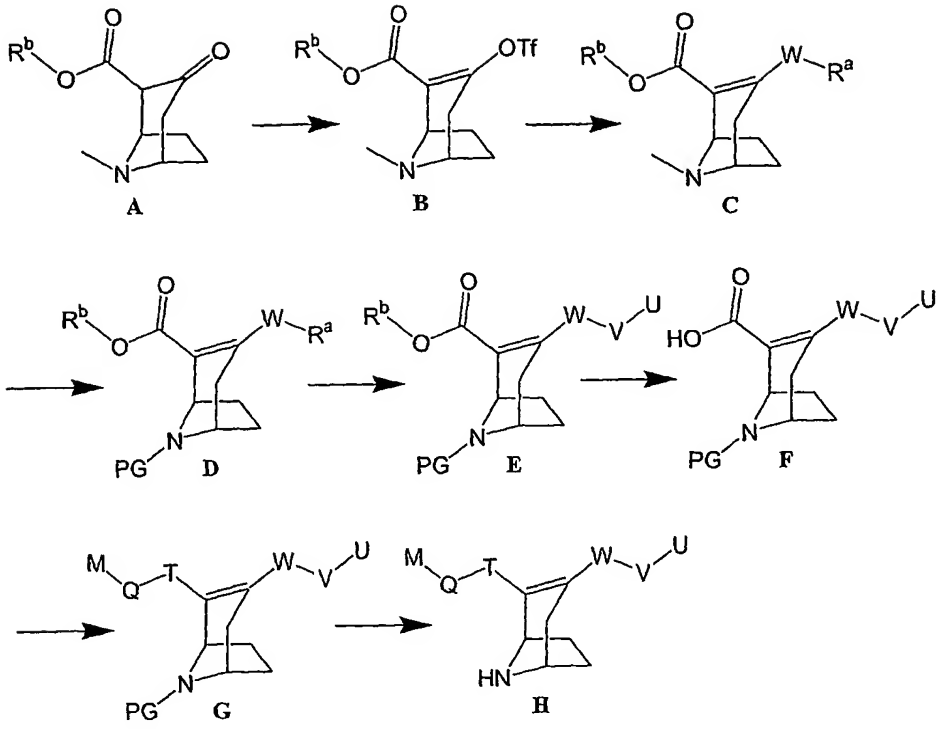
The compounds of formula **I** may also be used in combination with one or more other pharmacologically active compounds e. g. with other renin inhibitors, with ACE-inhibitors, angiotensin II receptor antagonists, endothelin receptor antagonists, vasodilators, calcium antagonists, potassium activators, diuretics, sympatholitics, beta-adrenergic antagonists, alpha-adrenergic antagonists, and neutral endopeptidase inhibitors, for the treatment of disorders as above-mentioned.

All forms of prodrugs leading to an active component comprised by general formula **I** above are included in the present invention.

The compounds of general formula **I** can be manufactured by the methods outlined below, by the methods described in the examples or by analogous methods.

Chemistry

Commercially available tropinone can be acylated racemically or enantioselectively as described in the literature (Majewski, M; *et al.*; *J. Org. Chem.*, **1995**, *60*, 5825). Then tropinone derivatives of type **A** (Scheme 1), whereas R^b typically represents a methyl, an ethyl or a benzyl group, may be transformed further accordingly to the chemistry described in earlier patent applications, for instance WO 03/093267 or WO 04/002957. For instance a compound of type **A** can be converted into a vinyl triflate of type **B**. A carbon-carbon coupling catalyzed by a metallic complex, like a palladium complex, can lead to a compound of type **C**, whereas R^a represents a substituent that can lead in one or several chemical maipulation to a substituent V-U as described in formula **I**. R^a can be modified during the synthesis. Protecting group manipulations can lead to a compound of type **D**. Well-known manipupulations at the R^a-substituent, like deprotection and *Mitsunobu* reaction, can lead to a compound of type **E**. Hydrolysis of the ester can lead to a compound of type **F**, then amide coupling to a compound of type **G**. Final deprotection can lead to a desired compound of type **H**.



The compounds of formula I and their pharmaceutically acceptable acid addition salts can be used as medicaments, e. g. in the form of pharmaceutical preparations for enteral, parenteral, or topical administration. They can be administered, for example, perorally, e. g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e. g. in the form of suppositories, parenterally, e. g. in the form of injection solutions or infusion solutions, or topically, e. g. in the form of ointments, creams or oils.

The production of pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and their pharmaceutically acceptable acid addition salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injections are, for example, water, alcohols, polyols, glycerols and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of compounds of formula I can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 mg to about 1000 mg, especially about 50 mg to about 500 mg, comes into consideration.

The pharmaceutical preparations conveniently contain about 1 - 500 mg, preferably 5 - 200 mg of a compound of formula I.

The following examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples

Abbreviations

ACE	Angiotensin Converting Enzyme
Ang	Angiotensin
aq.	aqueous
Boc	*tert*-Butyloxycarbonyl
BSA	Bovine serum albumine
BuLi	*n*-Butyllithium
DIPEA	Diisopropylethylamine
DMAP	4-*N,N*-Dimethylaminopyridine
DMSO	Dimethylsulfoxide
EDC·HCl	Ethyl-*N,N*-dimethylaminopropylcarbodiimide hydrochloride
EIA	Enzyme immunoassay
eq.	equivalent
Et	Ethyl
EtOAc	Ethyl acetate
FC	Flash Chromatography
HOBt	Hydroxybenzotriazol
MeOH	Methanol
NMO	*N*-Methylmorpholine *N*-oxide
org.	organic
PG	protecting group
Ph	Phenyl
RAS	Renin Angiotensin System
rt	room temperature
sol.	Solution
TBDMS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethylsulfonyl
THF	Tetrahydrofuran

Precursors

(*rac.*)-(*1R, *5S**)-8-Methyl-3-trifluoromethanesulfonyloxy-8-azabicyclo-[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (B)**

A sol. of compound **A** (1.81 g, 9.12 mmol) in THF (35 mL) was cooled to 0 °C and NaH (about 60% in mineral oil, 435 mg, about 10.0 mmol) was added. A gas evolution was observed. After 20 min, Tf_2NPh (3.86 g, 10.8 mmol) was added. 10 min later, the ice bath was removed. The sol. was stirred overnight, and diluted with EtOAc and washed with brine (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC yielded the title compound (2.37 g, 78%).

(*rac.*)-(*1R, *5S**)-3-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-8-methyl-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (C)**

A sol. of [3-(4-bromophenyl)propoxy]-*tert*-butyldimethylsilane (Kiesewetter D. O., *Tetrahedron Asymmetry*, **1993**, *4*, 2183, 16.47 g, 50.0 mmol) in THF (250 mL) was cooled to -78 °C. BuLi (1.6M in hexane, 31.0 mL, 50.0 mmol) was added. After 30 min, $ZnCl_2$ (1M in THF, 52 mL, 52 mmol, prepared from $ZnCl_2$ dried overnight at 150 °C and THF) was added. The mixture was allowed to warm up to rt. Vinyl triflate **B** (7.90 g, 24.0 mmol) in THF (20 mL) and then $Pd(PPh_3)_4$ (500 mg, 0.43 mmol) were added. The mixture was heated tro reflux for 90 min and aq. 1M HCl (1 mL) was added. The mixture was diluted with EtOAc and washed with aq. 1M NaOH (1x). The org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title product (8.44 g, 82%).

(*rac.*)-(*1R, *5S**)-3-[4-(3-Hydroxypropyl)phenyl]-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester 2-methyl ester (D)**

1–Chloroethyl chloroformate (7.98 g, 56.0 mmol) was added to a sol. of bicyclooctene **C** (8.07 g, 18.8 mmol) in 1,2-dichloroethane (120 mL). The sol. was heated to reflux. After 4 h, the reaction mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. MeOH (100 mL) was added. The mixture was stirred at 75 °C for 30 min, and the solvents were removed under reduced pressure. The residue was diluted with EtOAc and washed with aq. 1M NaOH (2x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was dissoled in CH_2Cl_2 (50 mL), DIPEA (4.70 g, 36.0 mmol) was added, and the mixture was cooled to 0 °C. Boc_2O (4.65 g, 21.0 mmol) was added and the mixture was stirred at 0 °C for 1 h, then at rt for 2 h. The mixture was washed with aq. 1M HCl (1x), and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (4.81 g, 64%).

(*rac.*)-(*1R, *5S**)-3-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-8-aza-bicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester 2-methyl ester (E1)**

Tributylphosphine (3.18 g, 14.0 mmol) was added to a sol. of bicyclooctene **D** (2.09 g, 5.2 mmol), 2,3,6-trifluorophenol (1.59 g, 10.7 mmol) and azodicarboxylic dipiperidide (2.70 g, 10.7 mmol) in toluene (50 mL). The mixture was heated to reflux for 2 h and allowed to cool to rt. The solvents were removed under reduced pressure. Purification by FC yielded the title compound (2.15 g, 78%).

(*rac.*)-(*1R, *5S**)-3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester 2-methyl ester (E2)**

Tributylphosphine (1.61 mL, 7.2 mmol) was added to a sol. of bicyclooctene **D** (1.04 g, 2.59 mmol), 2-chloro-3,6-trifluorophenol (833 mg, 5.10 mmol) and azodicarboxylic dipiperidide (1.29 g, 5.10 mmol) in toluene (25 mL). The

mixture was heated to reflux for 2 h and allowed to cool to rt. The solvents were removed under reduced pressure. Purification by FC yielded the title compound (1.11 g, 78%).

(*rac.*)-(*1R, *5S**)-3-{4-[3-(4-Fluoro-5-methylisoxazol-3-yloxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester 2-methyl ester (E3)**

Tributylphosphine (13.72 mL, 47.4 mmol) was added to a sol. of bicyclocteneD (6.34 g, 15.8 mmol), 4-fluoro-5-methylisoxazol-3-ol (Nakayama, E.; Watanabe, K.; Miyauchi, M.; Fujimoto, K.; Ide, *J. of Antibiotics*, **1990**, *43*, 1122, 2.77, 23.7 mmol) and azodicarboxylic dipiperidide (5.98 g, 31.6 mmol) in toluene (25 mL). The mixture was heated to reflux for 2 h and allowed to cool to rt. The solvents were removed under reduced pressure. Purification by FC yielded the title compound (6.05 g, 76%).

(*rac.*)-(*1R, *5S**)-3-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-8-aza-bicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester (F1)**

Bicycloctene **E1** (1.75 g, 3.29 mmol) was dissolved in EtOH (30 mL). Aq. 1M NaOH (30 mL) was added and the mixture was heated to 80 °C. The sol. was stirred for 5 h at 80 °C, then allowed to cool down to rt. After acidification to pH = 1-2 with aq. 1M HCl the mixture was extracted with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (1.78 g, quantitative).

(*rac.*)-(*1R, *5S**)-3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester (F2)**

Bicycloctene **E2** (2.42 g, 4.40 mmol) was dissolved in EtOH (50 mL). Aq. 1M NaOH (40 mL) was added and the mixture was heated to 80 °C. The sol. was

stirred for 5 h at 80 °C, then allowed to cool down to rt. After acidification to pH = 1-2 with aq. 1M HCl the mixture was extracted with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (2.48 g, quantitative).

(*rac.*)-(*1R, *5S**)-3-{4-[3-(4-Fluoro-5-methylisoxazol-3-yloxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester (F3)**

Bicyclooctene **E3** (6.05 g, 12.08 mmol) was dissolved in EtOH (115 mL). Aq. 1M NaOH (90 mL) was added and the mixture was heated to 80 °C. The sol. was stirred for 5 h at 80 °C, then allowed to cool down to rt. After acidification to pH = 1-2 with aq. 1M HCl the mixture was extracted with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (4.98 g, 84%).

Examples

Example 1

(*rac.*)-(*1R, *5S**)-3-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide**

A mixture of bicyclononene **F1** (0.89 g, 1.70 mmol), cyclopropyl-(2,3-dichloro-benzyl)amine (1.08 g, 5.00 mmol), DIPEA (0.87 gL, 6.70 mmol), DMAP (60 mg, 0.50 mmol), HOBt (137 mg, 1.00 mmol) and EDC·HCl (0.96 g, 5.00 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 3 days. The mixture was diluted with more CH_2Cl_2, and washed with aq. 1M HCl (3x) and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the intermediate

compound. This intermediate compound was diluted with CH_2Cl_2 (10 mL) and the mixture was cooled to 0 °C. HCl (4M in dioxane, 10 mL) was added and the mixture was stirred for 1 h at 0 °C, then 1h at rt. The solvents were removed under reduced pressdure and the residue was dried under high vacuum. The residue was diluted with CH_2Cl_2 and washed with aq. 1M NaOH until the org. phase had a pH > 9. The org. extracts wer dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (497 mg).

Example 2

(*rac.*)-(*1R, *5S**)-3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide**

A mixture of bicyclononene **F2** (2.01 g, 3.70 mmol), cyclopropyl-(2,3-dichloro-benzyl)amine (2.43 g, 11.2 mmol), DIPEA (2.07 g, 16.0 mmol), DMAP (135 mg, 1.10 mmol), HOBt (486 mg, 3.60 mmol) and EDC·HCl (2.49 g, 13.0 mmol) in CH_2Cl_2 (30 mL) was stirred at rt for 3 days. The mixture was diluted with more CH_2Cl_2, and washed with aq. 1M HCl (3x) and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the intermediate compound. This intermediate compound was diluted with CH_2Cl_2 (10 mL) and the mixture was cooled to 0 °C. HCl (4M in dioxane, 10 mL) was added and the mixture was stirred for 1 h at 0 °C, then 1h at rt. The solvents were removed under reduced pressdure and the residue was dried under high vacuum. The residue was diluted with CH_2Cl_2 and washed with aq. 1M NaOH until the org. phase had a pH > 9. The org. extracts wer dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (1.35 g).

Example 3

(*rac.*)-(*1R, *5S**)-3-{4-[3-(4-Fluoro-5-methylisoxazol-3-yloxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide**

A mixture of bicyclononene **F3** (2.50 g, 5.14 mmol), cyclopropyl-(2-methyl-3-methoxybenzyl)amine (prepared by reductive amination from 3-methoxy-2-methylbenzaldehyde, Comins, D. L.; Brown, J. D., *J. Org. Chem.*, **1989**, *54*, 3730, and cyclopropylamine; 2.95 g, 15.4 mmol), DIPEA (3.52 mL, 20.6 mmol), DMAP (157 mg, 1.29 mmol), HOBt (903 mg, 6.69 mmol) and EDC·HCl (2.47 g, 12.9 mmol) in CH_2Cl_2 (30 mL) was stirred at rt for 3 days. The mixture was diluted with more CH_2Cl_2, and washed with aq. 1M HCl (3x) and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the intermediate compound. This intermediate compound was diluted with CH_2Cl_2 (10 mL) and the mixture was cooled to 0 °C. HCl (4M in dioxane, 10 mL) was added and the mixture was stirred for 1 h at 0 °C, then 1h at rt. The solvents were removed under reduced pressdure and the residue was dried under high vacuum. The residue was diluted with CH_2Cl_2 and washed with aq. 1M NaOH until the org. phase had a pH > 9. The org. extracts wer dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (1.54 g).

Inhibition of human recombinant renin by the compounds of the invention

The enzymatic in vitro assay was performed in 384-well polypropylene plates (Nunc). The assay buffer consisted of 10 mM PBS (Gibco BRL) including 1 mM EDTA and 0.1% BSA. The incubates were composed of 50 µL per well of an enzyme mix and 2.5 µL of renin inhibitors in DMSO. The enzyme mix was premixed at 4°C and consists of the following components:

• human recombinant renin (0.16 ng/mL) • synthetic human angiotensin(1-14) (0.5 µM)

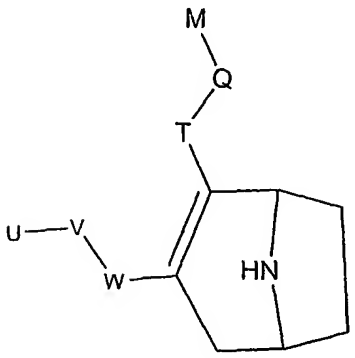
• hydroxyquinoline sulfate (1 mM)

The mixtures were then incubated at 37°C for 3 h.

To determine the enzymatic activity and its inhibition, the accumulated Ang I was detected by an enzyme immunoassay (EIA) in 384-well plates (Nunc). 5 µL of the incubates or standards were transferred to immuno plates which were previously coated with a covalent complex of Ang I and bovine serum albumin (Ang I – BSA). 75 µL of Ang I-antibodies in essaybuffer above including 0.01% Tween 20 were added and a primary incubation made at 4 °C overnight. The plates were washed 3 times with PBS including 0.01% Tween 20, and then incubated for 2 h at rt with an antirabbit-peroxidase coupled antibody (WA 934, Amersham). After washing the plates 3 times, the *peroxidase substrate* ABTS (2.2'-azino-di-(3-ethyl-benzthiazolinsulfonate), was added and the plates incubated for 60 min at room temperature. After stopping the reaction with 0.1 M citric acid pH 4.3 the plate was evaluated in a microplate reader at 405 nm. The percentage of inhibition was calculated of each concentration point and the concentration of renin inhibition was determined that inhibited the enzyme activity by 50% (IC_{50}). The IC_{50}-values of all compounds tested are below 100 nM. However selected compounds exhibit a very good bioavailibility and are metabolically more stable than prior art compounds.

Claims

1. Compounds of the general formula **I**



General formula **I**

wherein

W is a six-membered, non benzofused, phenyl or heteroaryl ring, substituted by V in *meta* or *para* position;

V represents a bond; -$(CH_2)_r$-; -A-$(CH_2)_s$-; -CH_2-A-$(CH_2)_t$-; -$(CH_2)_s$-A-; -$(CH_2)_2$-A-$(CH_2)_u$-; -A-$(CH_2)_v$-B-; -CH_2-CH_2-CH_2-A-CH_2-; -A-CH_2-CH_2-B-CH_2-; -CH_2-A-CH_2-CH_2-B-; -CH_2-CH_2-CH_2-A-CH_2-CH_2-; -CH_2-CH_2-CH_2-CH_2-A-CH_2-; -A-CH_2-CH_2-B-CH_2-CH_2-; -CH_2-A-CH_2-CH_2-B-CH_2-; -CH_2-A-CH_2-CH_2-CH_2-B-; -CH_2-CH_2-A-CH_2-CH_2-B-; -O-CH_2-$CH(OCH_3)$-CH_2-O-; -O-CH_2-$CH(CH_3)$-CH_2-O-; -O-CH_2-$CH(CF_3)$-CH_2-O-; -O-CH_2-$C(CH_3)_2$-CH_2-O-; -O-CH_2-$C(CH_3)_2$-O-; -O-$C(CH_3)_2$-CH_2-O-; -O-CH_2-$CH(CH_3)$-O-; -O-$CH(CH_3)$-CH_2-O-; -O-CH_2-$C(CH_2CH_2)$-O-; or -O-$C(CH_2CH_2)$-CH_2-O-;

A and B independently represent -O-; -S-; -SO-; -SO_2-;

U represents aryl; heteroaryl;

T represents -$CONR^1$-; -$(CH_2)_pOCO$-; -$(CH_2)_pN(R^1)CO$-; -$(CH_2)_pN(R^1)SO_2$-; or

-COO-;

Q represents lower alkylene; lower alkenylene;

M represents hydrogen; cycloalkyl; aryl; heterocyclyl; heteroaryl;

R^1 represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

p is the integer 1, 2, 3 or 4;
r is the integer 3, 4, 5, or 6;
s is the integer 2, 3, 4, or 5;
t is the integer 1, 2, 3, or 4;
u is the integer 1, 2, or 3;
v is the integer 2, 3, or 4;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

2. Compounds of general formula I according to claim 1 wherein W, V, and U are as defined in general formula I and

Γ represents -$CONR^1$-;
Q represents methylene;
M aryl; heteroaryl;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

3. Compounds of general formula **I** according to claim 1 wherein W, U, T, Q, and M are as defined in general formula **I** and

V represents $-CH_2CH_2O-$; $-CH_2CH_2CH_2O-$; $-OCH_2CH_2O-$;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

4. Compounds of general formula **I** according to claim 1 wherein V, U, T, Q, and M are as defined in general formula **I** and

W represents a 1,4-disubstituted phenyl group;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

5. Compounds of general formula **I** according to claim 1 wherein W, V, Q, T, and M are as defined in general formula **I** and

U is a mono-, di-, or trisubstituted phenyl or heteroaryl, whereby the substituents are halogen, lower alkyl, lower alkoxy, CF_3

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

6. The compounds according to any one of claims 1 to 5 selected from the group consisting of

(*rac.*)-(*1R**, *5S**)-3-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-8-azabicyclo-[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*rac.*)-(*1R**, *5S**)-3-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*rac.*)-(*1R**, *5S**)-3-{4-[3-(4-fluoro-5-methylisoxazol-3-yloxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(3-methoxy-2-methyl-benzyl)amide.

7. Pharmaceutical compositions containing at least one compound of any ones of claims 1 to 6 and usual carrier materials and adjuvants for the treatment or prophylaxis of disorders which are associated with a dysregulation of the renin-angiotensin system (RAS), comprising cardiovascular and renal diseases, hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppressive agents after organ transplantation, and other diseases known to be related to the RAS.

8. A method for the treatment or prophylaxis of diseases which are related to the RAS comprising hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppressive agents after organ transplantation, and other diseases which are related to the RAS, which method

comprises administering a compound according to any one of claims 1 to 6 to a human being or animal.

9. The use of compounds according to any one of claims 1 to 6 for the treatment or prophylaxis of diseases which are associated with the RAS comprising hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppressive agents after organ transplantation, and other diseases known to be related to the RAS.

10. The use of one or more compounds of any one of claims 1 to 6 in combination with other pharmacologically active compounds comprising ACE inhibitors, angiotensin II receptor antagonists, endothelin receptor antagonists, vasodilators, calcium antagonists, potassium activators, diuretics, sympatholitics, beta-adrenergic antagonists, alpha-adrenergic antagonists, and neutral endopeptidase inhibitors, for the treatment of disorders as set forth in any one of claims 7 to 10.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/004375

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D451/02 A61K31/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 051 712 A (MAERKI HANS-PETER ET AL) 18 April 2000 (2000-04-18) column 1, line 7 - column 3, line 21 column 51, lines 9-27	1-10
A	US 3 509 161 A (DOLD OTTO ET AL) 28 April 1970 (1970-04-28) column 2, line 49 - column 3, line 7	1-10
A	US 2002/188003 A1 (CARROLL FRANK IVY ET AL) 12 December 2002 (2002-12-12) claim 1	1-10
A	US 2003/013883 A1 (BALDWIN RONALD MARTIN ET AL) 16 January 2003 (2003-01-16) abstract claim 1	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 August 2004	01/09/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Samsam Bakhtiary, M

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/004375

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 8 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/004375

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6051712 A	18-04-2000	US 6150526 A	21-11-2000
		AT 242213 T	15-06-2003
		AU 708616 B2	05-08-1999
		AU 6743296 A	27-03-1997
		BR 9610385 A	06-07-1999
		CA 2230931 A1	13-03-1997
		CN 1202152 A	16-12-1998
		CZ 9800684 A3	14-10-1998
		DE 59610509 D1	10-07-2003
		DK 863875 T3	01-12-2003
		WO 9709311 A1	13-03-1997
		EP 0863875 A1	16-09-1998
		ES 2201192 T3	16-03-2004
		HU 9900926 A2	28-09-1999
		IL 123293 A	24-06-2003
		JP 11500447 T	12-01-1999
		MA 23967 A1	01-04-1997
		NO 980954 A	28-04-1998
		NZ 315677 A	28-02-2000
		PL 325425 A1	20-07-1998
		PT 863875 T	31-10-2003
		RU 2167865 C2	27-05-2001
		TR 9800409 T1	21-05-1998
		TW 474932 B	01-02-2002
		ZA 9607424 A	07-03-1997
US 3509161 A	28-04-1970	NONE	
US 2002188003 A1	12-12-2002	US 5736123 A	07-04-1998
		US 5496953 A	05-03-1996
		US 5128118 A	07-07-1992
		US 5413779 A	09-05-1995
		AU 650059 B2	09-06-1994
		AU 8519591 A	02-03-1992
		CA 2089070 A1	10-02-1992
		DE 69123151 D1	19-12-1996
		EP 0542903 A1	26-05-1993
		GR 3022529 T3	31-05-1997
		JP 3350049 B2	25-11-2002
		JP 6503556 T	21-04-1994
		US 6329520 B1	11-12-2001
		US 6531483 B1	11-03-2003
		US 2003023090 A1	30-01-2003
		US 2003203934 A1	30-10-2003
		US 5935953 A	10-08-1999
		US 6123917 A	26-09-2000
		AT 182794 T	15-08-1999
		AU 668371 B2	02-05-1996
		AU 3064592 A	15-06-1993
		CA 2123570 A1	27-05-1993
		DE 69229744 D1	09-09-1999
		DE 69229744 T2	27-04-2000
		DK 644775 T3	06-03-2000
		EP 0644775 A1	29-03-1995
		EP 0897922 A2	24-02-1999
		EP 0905135 A2	31-03-1999
		ES 2138601 T3	16-01-2000
		FI 942231 A	13-05-1994

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/004375

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002188003 A1		GR 3031579 T3	31-01-2000
		JP 2852467 B2	03-02-1999
		JP 7501074 T	02-02-1995
		KR 251339 B1	01-09-2000
		NO 941753 A	10-05-1994
		WO 9309814 A1	27-05-1993
		US 5380848 A	10-01-1995
		AT 145140 T	15-11-1996
		DK 542903 T3	21-04-1997
		ES 2099167 T3	16-05-1997
		WO 9202260 A1	20-02-1992
US 2003013883 A1	16-01-2003	NONE	